Pharmacotherapy of Alcohol Dependence: Approved Medications

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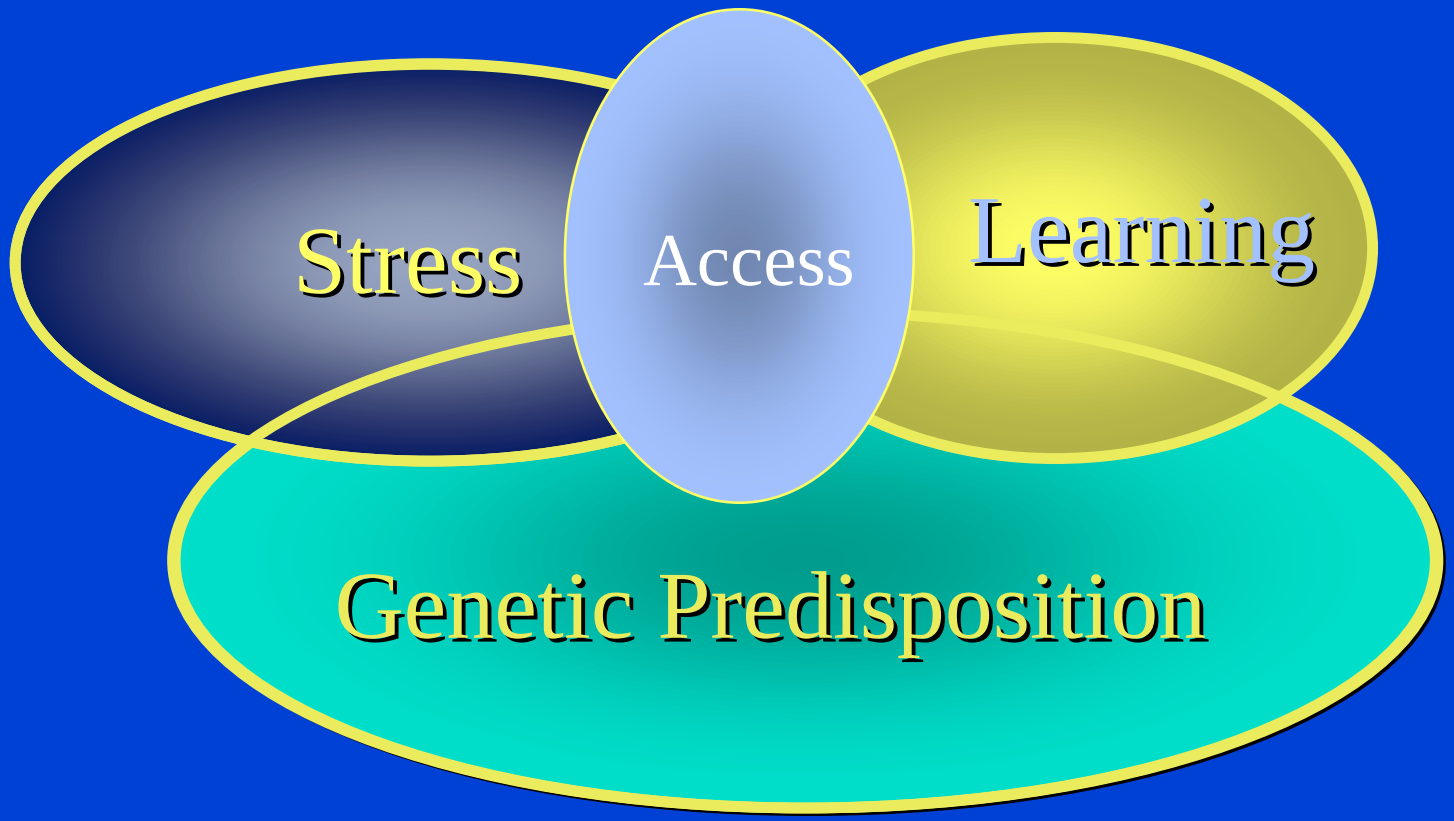
Alcohol and Drug Dependence



Pharmacotherapy for Alcohol Dependence

- Medications that deter drinking [disulfiram]
- Medications that reduce the motivation to drink heavily [naltrexone, nalmefene]
- Medications that treat co-existing psychiatric conditions [buspirone, fluoxetine, sertraline,]

Disulfiram

- MECHANISM OF ACTION
- EFFICACY
- ADVERSE EFFECTS
- COMPLIANCE

Disulfiram Treatment: History and Mechanism

- First described in 1938: Akron rubber workers using disulfiram as curing agent became ill after drinking. Similar report 1947 in Denmark among researchers who drank after testing it as an antihelminthic
- Irreversible inhibitor of aldehyde dehydrogenase, which catalyzes 2nd reaction of ethanol degradation:

  ethanol -------> acetaldehyde --------> acetate

  thus resulting in elevated levels of acetaldehyde, a potent dilator of arterial and capillary tone, producing decreased blood pressure, flushing, headache, and dizziness
- At high concentration inhibits dopamine beta hydroxylase, which elevates dopamine levels, and may produce psychosis

Disulfiram Treatment: CNS Mechanism

- PET study evaluated effect of disulfiram on ICMRglu [FdG glucose metabolism scan] and 11C- flumazenil [Bz receptor binding] effects in 48 male alcoholics, 11 of whom were taking disulfiram
- FdG: Significantly decreased global FdG uptake in D-treated pts.
- Decreased flumazenil influx and distribution volume in D-treated pts.

Gilman, et al. 1996

Disulfiram: Efficacy

- Fuller et al. VA study: Increases abstinent days and decreases heavy drinking days, but no clear evidence of prolonged abstinence. High non-compliance rates
- O'Farrell: Spousal contracts markedly increase compliance. Pt. takes disulfiram daily before spouse. Each thank other. Spouse doesn't discuss prior drinking problems. Spouse calls MD only if > 2 days missed.
- No evidence of efficacy of disulfiram implants

Disulfiram and Acamprosate

Multicenter European study of acamprosate [A] in chronic or episodic alcohol dependence.

118 S's in RCT of PBO vs A, with 360 d. Tx and 360 d. f/u
S's stratified for concomitant voluntary use of disulfiram [D].

A superior to PBO in PDA days and duration abst. x 4 mos.
No adverse interaction between A and D occurred
Subgroup who received both D and A had longer continuous abstinence than on either Rx alone.

Besson et al. 1998

Disulfiram in Cocaine Dependence

- 122 mixed cocaine/alcohol dependent subjects in urban clinic [27% F, 67% non-caucasian]
- 12 week RCT of CBT plus Disulfiram [D] [250mgQD];

  TSF +D; CM + D; CBT alone; TSF alone
- D associated with significantly better retention in treatment, longer duration of abstinence from alcohol and cocaine.
- CBT and TSF were associated with reduced cocaine use than CM.
- Cocaine and alcohol use strongly related throughout treatment, especially with disulfiram Rx

Carroll et al. 1998

Disulfiram in Cocaine Dependence

- Drinking often a precursor to cocaine use
- 67 cocaine dependent subjects in MMT [52% F, 51% Cauc.]
- 12 week double-blind, PBO controlled clinical trial of 250 mg disulfiram QD
- Significant reduction in cocaine use by disulfiram-treated than PBO-treated subjects
- Minimal drinking by either group

Petrakis et al. 2000

PRIMUM NON NOCERE

Disulfiram: Safety

- **Disulfiram Ethanol Reaction:** consumption of ethanol produces increased acetaldehyde, yielding vasodilation, HA, - HR, nausea, shock, death. Phentolamine reverses. **Contraindicated in patients with severe cardiovascular disease.**
- **Common adverse events: drowsiness, headache, sleepiness, garlic breath**
- **Rare AE's: Dose-related: neuropathy [axonal, after 5-6 months, reversible, < 50 cases, F > M], confusion, optic neuritis, & psychosis [risks: mood disorder and schiz.], fatal hepatitis [risk: 1/30K], allergy [ask about rubber allergy]**
- **Disulfiram inhibits CYP2E1: potential for drug interactions**

Disulfiram: Enhancing Compliance

3 options

- **Written contract,** such as in BMT: provides instructions about contract benefits, methods to establish habitual daily disulfiram use, and specifying that the alcoholic will take disulfiram daily under spouse/S.O. observation, couple then mutually thank each other, and refrain from arguments or discussions about the alcoholic's drinking;

- **The CRA disulfiram contract,** which is identical to above except that talk about drinking is not prohibited

- **Supervised disulfiram w/o a written contract, special instructions, or explicit verbal thanking.**

Disulfiram: BMT and Antabuse Contracts to Enhance Compliance

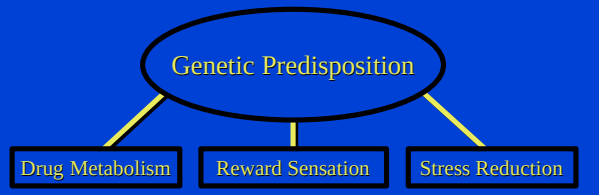
Disulfiram contract w/ Behavioral Marital Therapy [BMT] compared with disulfiram w/ couples or individual counseling.

- **Better compliance and reduced drinking during 3 months of active BMT**
- **These BMT drinking results eroded because of disulfiram contract discontinuation after (O'Farrell et al. 1985, 1992).**
- **BOOSTER SESSIONS: Compared with BMT alone, adding couples RP sessions after BMT improved contract compliance and drinking and marital outcomes.**
- **These better RP outcomes persisted for 18 to 24 months after BMT, especially for those with more severe drinking and marital problems (O'Farrell et al. 1993).**

OPIOID ANTAGONISTS

- RATIONALE
- EFFICACY
- MECHANISM OF ACTION
- ADVERSE EFFECTS
- RESPONSE PREDICTORS
- COMPLIANCE

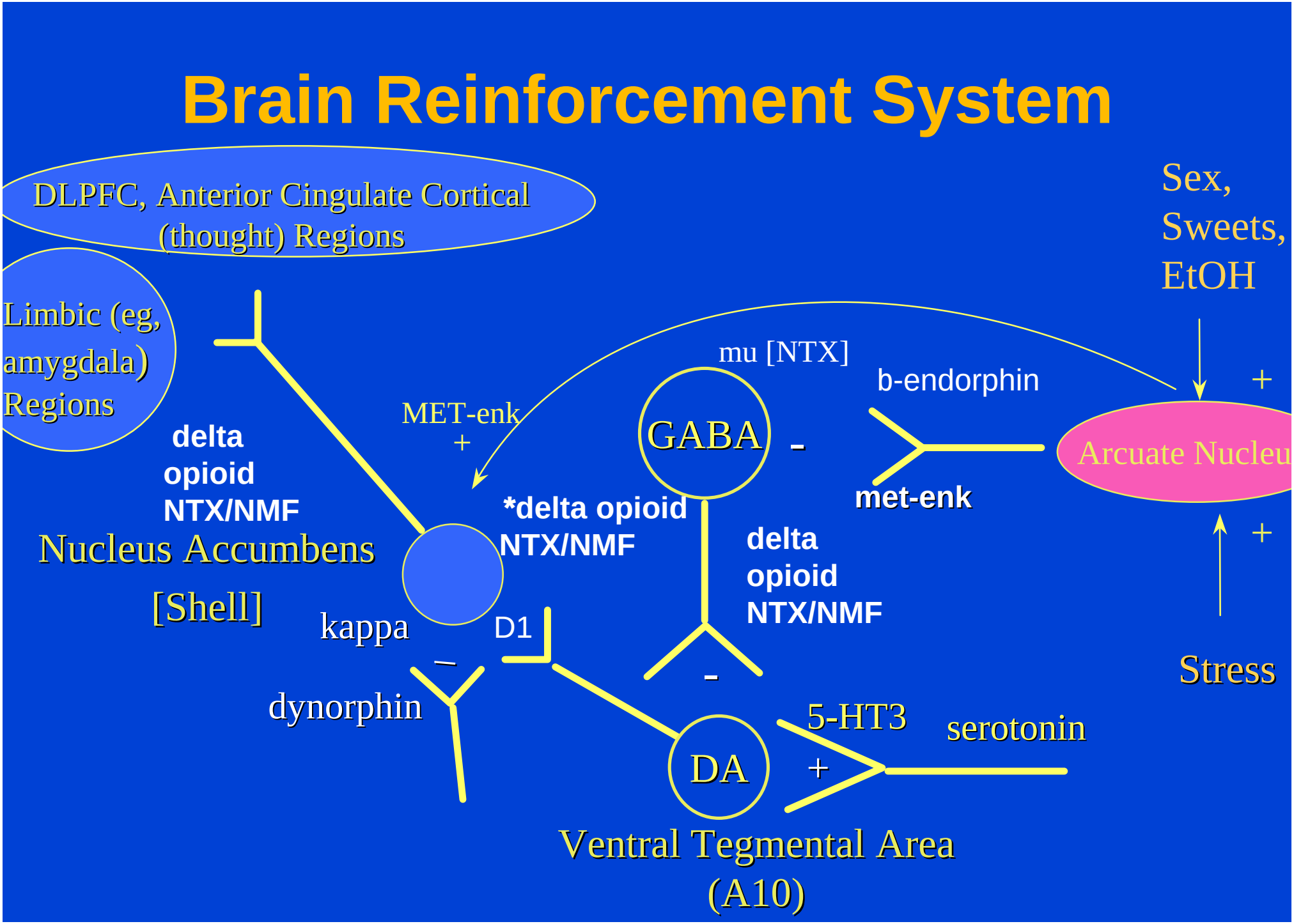
Alcohol Drinking & Opioids: Genetics



- HUMANS
  - High risk (FHP) have lower basal beta-endorphin than do low risk (FHN)
  - However, 0.05g% EtOH BAC --> greater rise in plasma beta-endorphin in high than low risk subjects
- RODENTS
  - Alcohol-preferring/high drinking strains synthesize and release more beta-endorphin than low-drinking strains, especially after EtOH dose
  - Mice lacking beta -endorphin gene drink less than controls


Old Style
Budweis

Brain Reinforcement System



Opioids, Reinforcement, and Alcohol Drinking

- Natural opiate peptides, endorphins and enkephalin, are positive CNS reinforcers of many behaviors
- Low dose opioids reinforce alcohol drinking
- Nonspecific [naloxone, naltrexone] and specific [mu, delta] opioid receptor antagonists block drinking reinforcement and reinforcement of drinking by rodents and monkeys
- Chronic EtOH increases [delta] opiate receptors and related intracellular responses [cyclic AMP]
- Chronic EtOH consumption and exposure increase CNS endorphin and enkaphalin opioid peptide release

Objectives: Naltrexone Clinical Trials

- To evaluate the effectiveness of naltrexone compared to placebo
- To evaluate the effect of different psychotherapeutic approaches in combination with naltrexone

Naltrexone Clinical Trials

- Volpicelli et al. 1992: VA patients; Day Treatment
- O'Malley et al. 1992: Outpatient M & F; Weekly CBT/CM
- Volpicelli et al. 1996: M and F Outpatients: RP therapy
- Anton et al. 1999: M and F Outpatients: CBT
- Others
- Ongoing: VA cooperative study, COMBINE

Study Design (O'Malley SS, et al, 1992)

Baseline

- ✓ Weekly efficacy and safety evaluation
- ✓ ASI at weeks 4, 8, and 12
- ✓ ALT and AST at weeks 4 and 12

ASI=Addiction Severity Index
ALT=alanine aminotransferase
AST=asparate aminotransferase

O'Malley SS, et al. *Arch Gen Psychiatry* 1992; 49:881-887

Cognitive Behavioral Therapy

- **Key Concept**
  - **Alcoholism represents a bad habit. It is a set of learned behaviors triggered by cues in the environment and aided by a constellation of dysfunctional automatic thoughts. The alcoholic has diminished control over drinking behavior and this can be brought under control.**

Cognitive Behavioral Therapy

- **Core Sessions**
  - Assessing high risk situations
  - Coping with cravings and urges to drink
  - Managing thoughts about alcohol
  - Problem solving
  - Drink refusal skills
  - Planning for emergencies
  - Seemingly irrelevant decisions
- **Now Excluded**
  - Abstinence violation effect

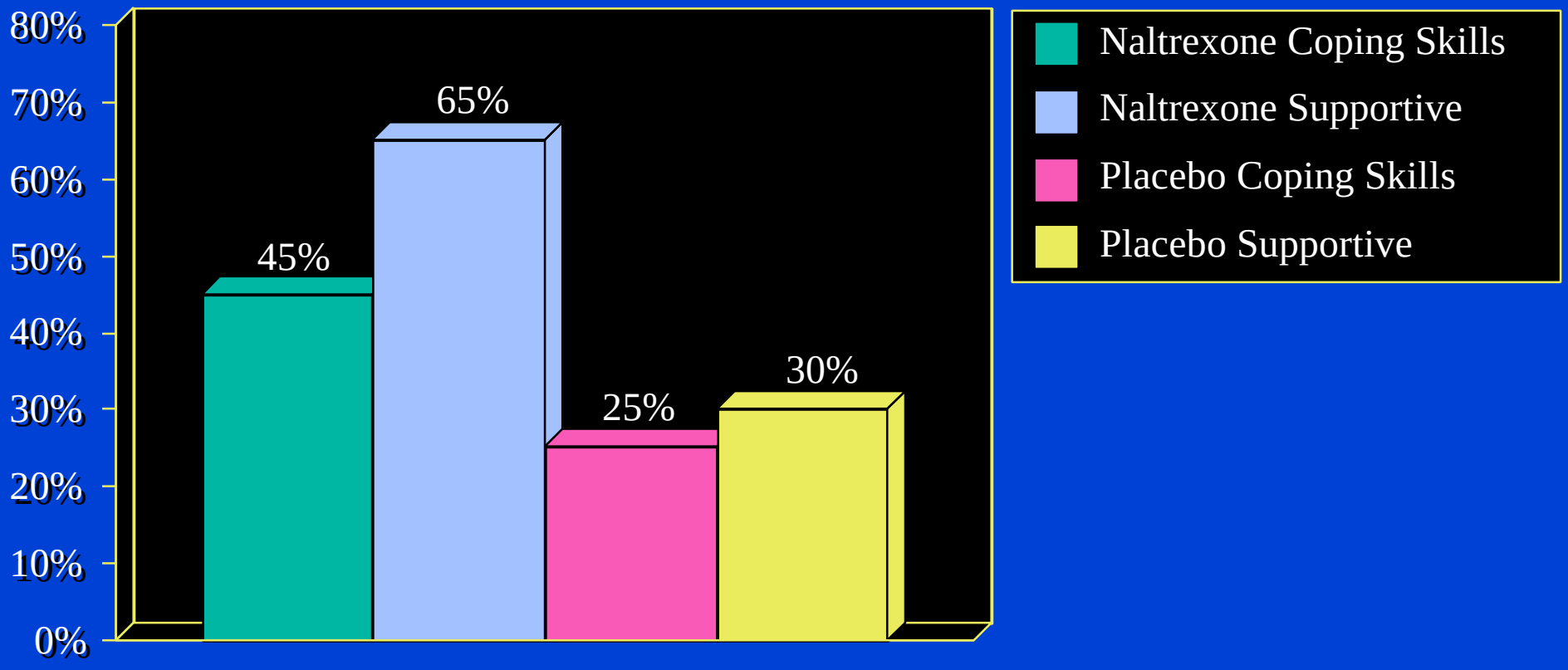
Project MATCH Manual Series, Vol 1
www.niaaa.nih.gov

Cognitive Behavioral Therapy Elective Sessions

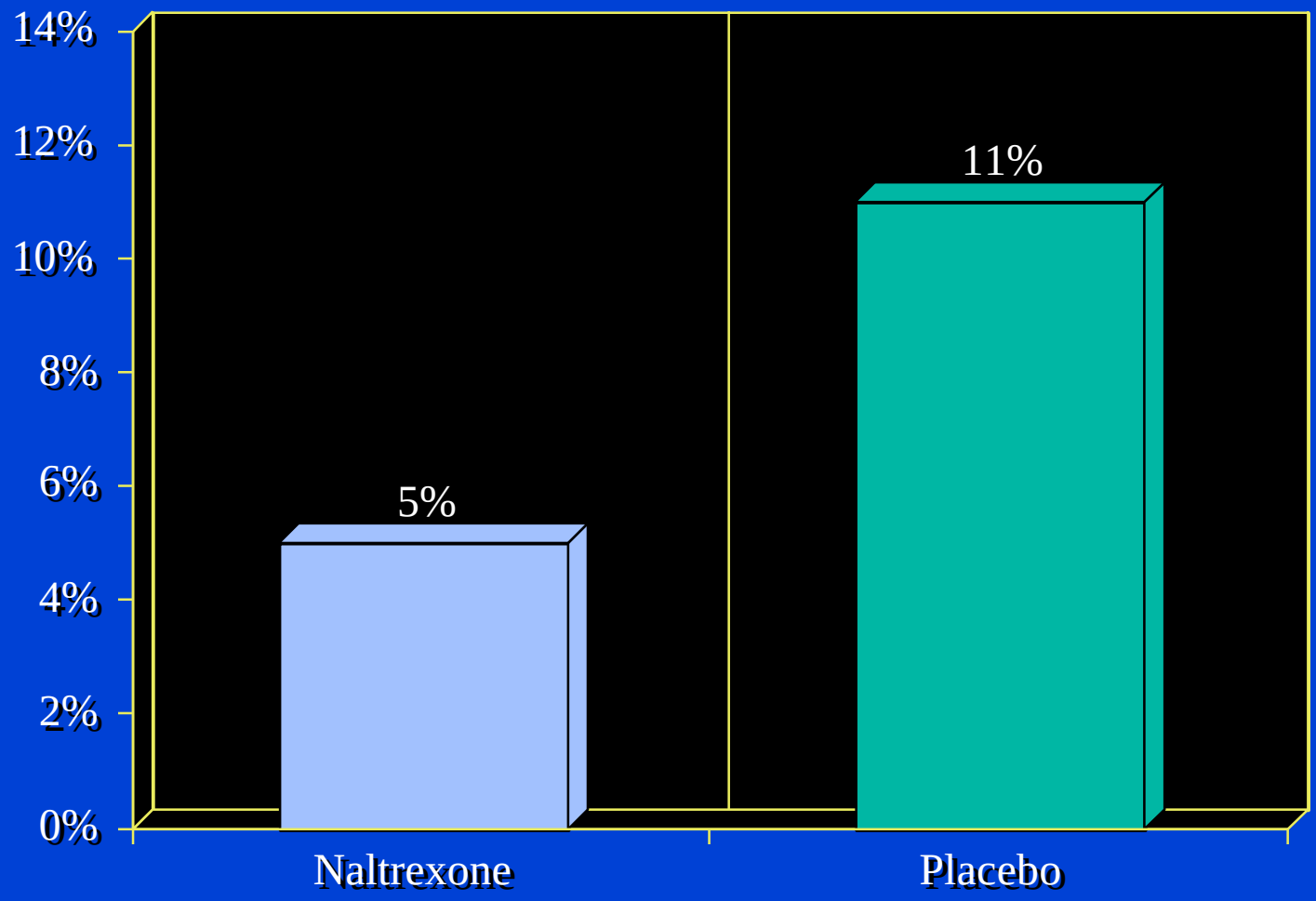
- **Topics Include**
  - Coping with anger
  - Managing negative thoughts and moods
  - Increasing pleasant activities
  - Enhancing social supports

Project MATCH Manual Series, Vol 1
www.niaaa.nih.gov

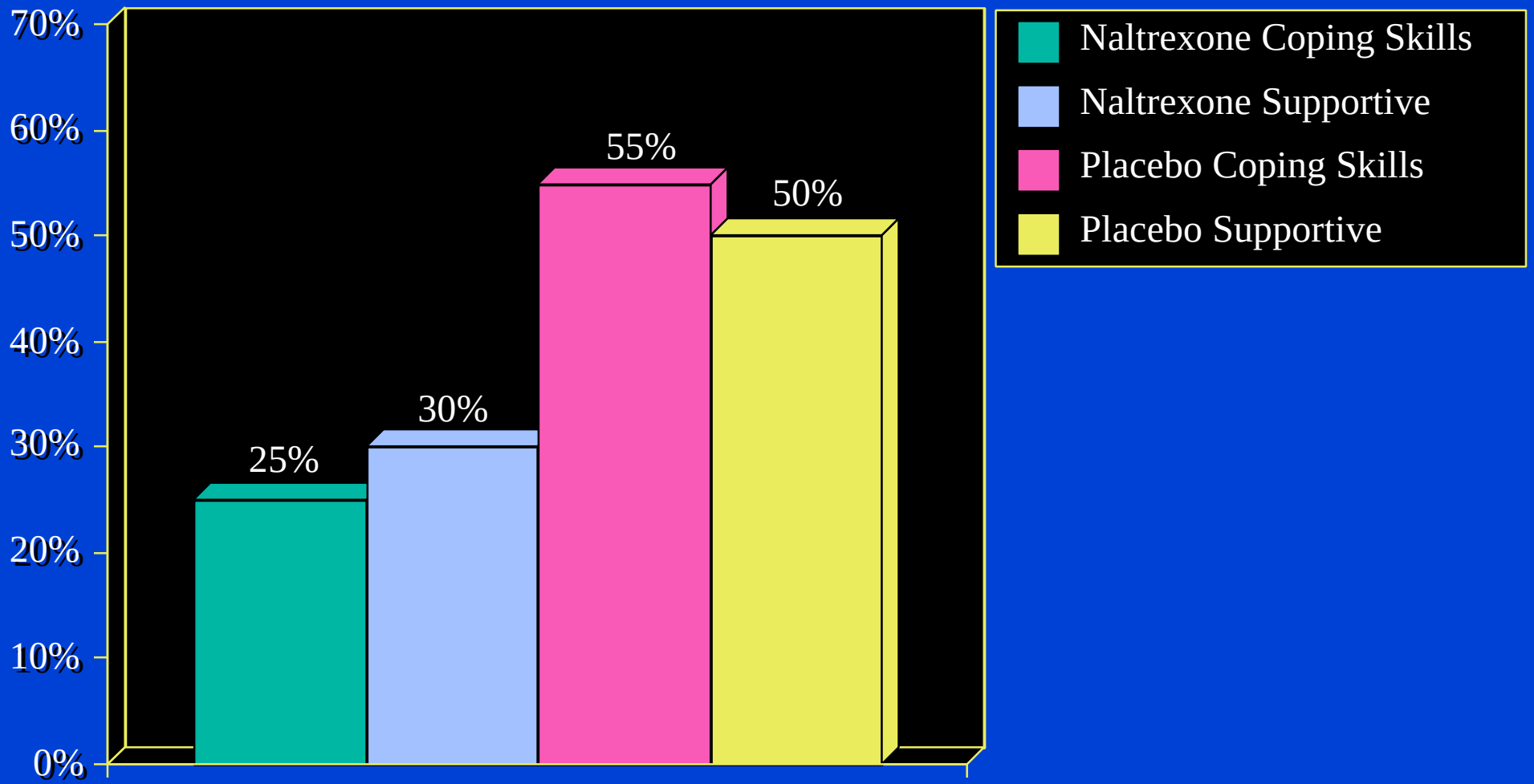
Abstinence Rates During Treatment



Percentage of Days on Which Alcohol was Consumed During Treatment (p<.01)



Relapse Rates During Treatment



Six Month Follow-up of NTX and Psychotherapy for Alcohol Dependence: Major Findings

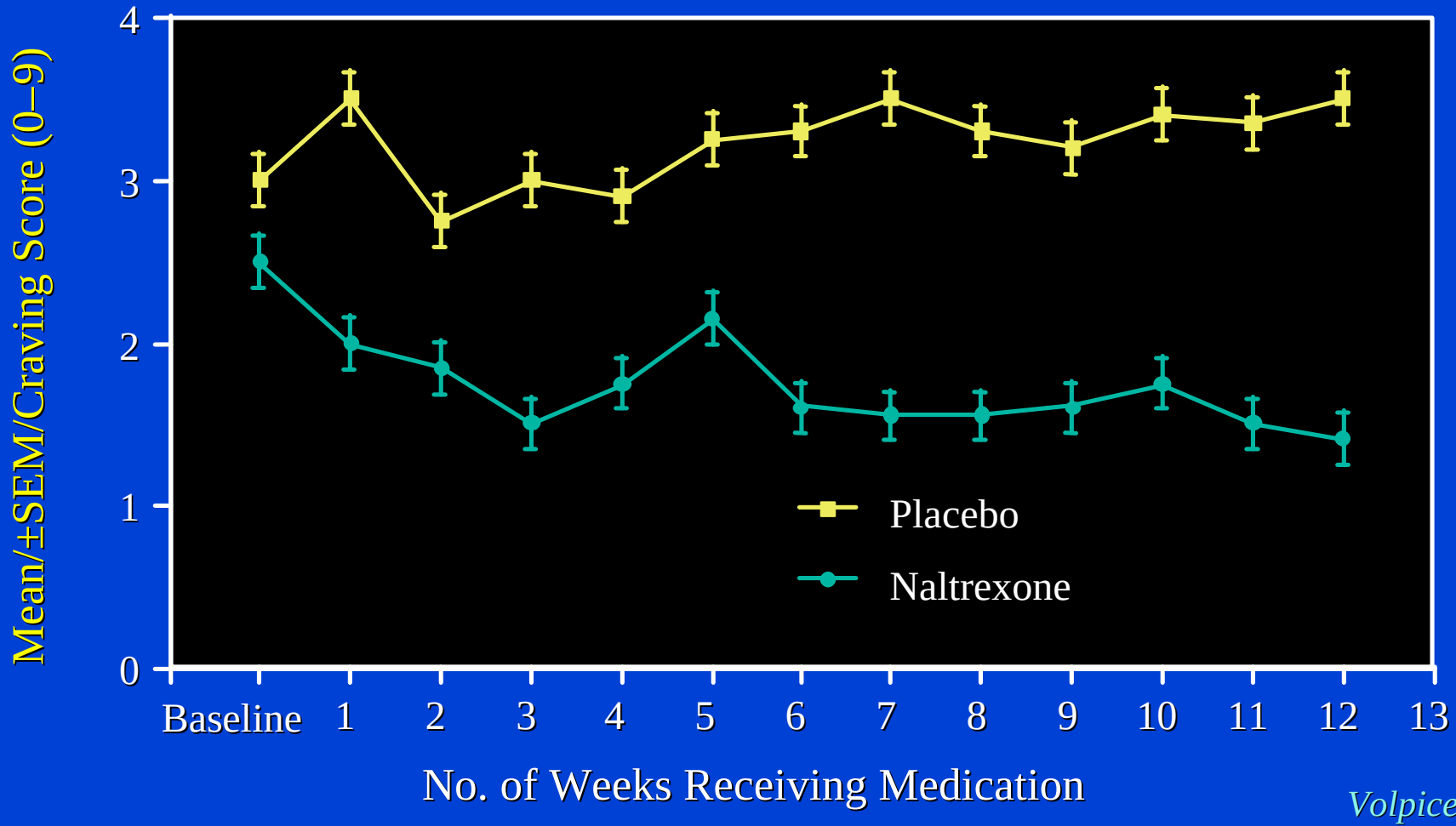
- 47% got post-study therapy; no Rx or Tx differences
- Post-tx abstinence: NTX > PBO only through month 1
- Post-tx heavy drinking ($\geq$ 5 M, $\geq$ 4 F) rates lower in NTX through month 5; CS = Sup Therapy
- On 3-level outcome [abst, light, heavy] drinking outcomes: NTX/CS > NTX/Sup $\geq$ PBO/CS > PBO/Sup; effect differences decreased with time
- NTX > PBO in preventing another episode of alcohol abuse or dependence sxs; CS = Sup Therapy

O'Malley et al, Arch Gen Psychiatry, 1996

Naltrexone and Alcohol Dependence: Negative Studies

- Mc Caul et al. : Polysubstance abusers
  - low compliance rates
- Chick et al.: Community dwelling alcoholics
  - low compliance rates
- Kranzler et al.: Community dwelling alcoholics
  - poor compliance, adverse effects, dropout

Mean Craving Scores for Naltrexone- and Placebo-Treated Groups



Volpicelli, 1992

Experience of a "slip": NTX vs. PBO

- **Compared with PBO-treatment, subjects receiving NTX reported, retrospectively**
  - **significantly lower intoxication, "high", and incoordination during the slip**
  - **similar pleasantness ratings and nausea rates**
  - **lower levels of pre-, within, and post-slip craving**
  - **more slip termination due to disincentive to drink**
  - **less slip termination due to adverse consequences**

Volpicelli et al., Am J Psychiatry, 1995; O'Malley et al., Am J Psychiatry, 1996

Naltrexone Prolongs Latency to Drink: Study Results

- NTX, compared with PBO and No Rx, significantly
  - increased latency to first drink
  - increased latency to second drink
  - reduced end-of-session BAC
  - increased fatigue and tension before drinking
  - increased nausea after alcohol
- NTX and other conditions not different in:
  - sip rate
  - drinking urges [no instructions to resist/avoid drinking]

Davidson Swift and Fitz Alc Clin Exp Res 1996

Naltrexone Effects on EtOH Responses: Role of Family Alcoholism History

29 young non-alcoholic regular drinkers ; 15 FHP

50 mg NTX x 1 week

Oral EtOH dose test session: Peak BAC: .06 g% [no FHx effect]

Subjective ratings

RESULTS

NTX dampened ratings of

--stimulation as BAC rose

--confusion as BAC fell [FHP subjects only]

King et al, Psychopharmacology 1997

Naltrexone: Effect on Drinking Behavior

- 51 young heavy drinkers treated with PBO and NTX for 7 d each in random order

NTX-treated S's

- had lower urges to consume alcohol
- took longer to finish each glass of beer
- were more likely to terminate beer drinking early
- Reported lower positive mood states and more nausea, headache after drinking

Davidson et al., 1999

Naltrexone Associated with Improved AST and GGT in Alcoholics

	Placebo		Naltrexone	
	Baseline	Week 12	Baseline	Week 12
AST, U/L	65.2±69.0	50.4±77.9	45.4±35.8	23.6±9.6
GGT, U/L	180.1±243.8	127.3±221.7	139.9±266.5	51.4±36.6

Volipcelli et al., AGP 1992

Percentage of Patients Who Withdrew Due to Side Effects

- 9.6% Naltrexone
- 1.9% Placebo

Multicenter Naltrexone Usage Safety Study

New-Onset Adverse Clinical Events Reported in ≥2% of Naltrexone-Treated Patients

Adverse Event	
Nausea	10%
Headache	7%
Dizziness	4%
Nervousness	4%
Fatigue	4%
Insomnia	3%
Vomiting	3%
Anxiety	2%
Somnolence	2%

Croop et al., Arch Gen Psychiatry 19

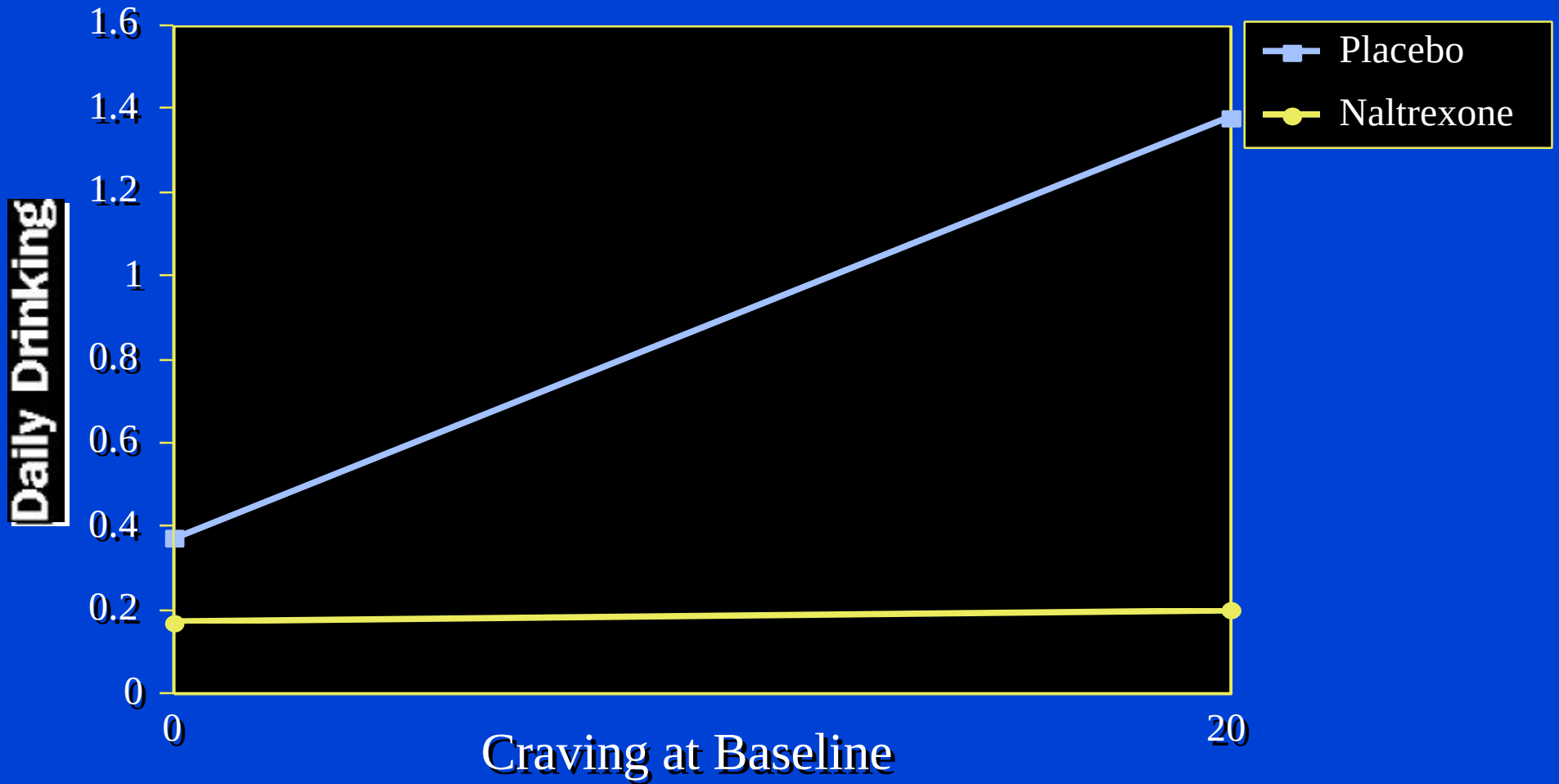
Naltrexone-Induced Nausea: Risk Factors

- 120 recently abstinent alcohol dependent S's in open label trial of 25 mg NTX QD x 7 d, then 50 mg NTX QD
- 15% had nausea

NTX-induced nausea associated with poor Rx compliance, heavier drinking during treatment, younger age, female gender, and, for lighter pre-treatment drinkers, shorter durations of abstinence.

O'Malley et al., 2000

NALTREXONE AND CRAVING: EFFECT ON DRINKING DURING TREATMENT



Naltrexone and Alcohol Dependence: Role of Subject Compliance

97 Alcohol dependent M & F randomized to 12 wks tx with NTX 50 mg or PBO daily, as well as RP counseling [Miller & Gorski] 2x [4wk], then 1x/week

RESULTS

NTX > PBO: relapse, days drinking, time to relapse. AST, GGT, high

% Relapse and % days drinking and time to relapse:

NTX > PBO in compliant subjects

NTX = PBO in non-compliant subjects

Volpicelli et al., Arch Gen Psychiatry 1997

Naltrexone and Alcoholism: Predictors of Clinical Efficacy

- High levels of baseline somatic distress
- High baseline levels of craving for alcohol
- Family history of alcoholism
- Low educational attainment [< HS]

Volpicelli et al., J Clin Psychiatry, 1995; Jaffe et al. JCCP, 1996; O'Malley et al., Am J Psychiatry, 1996

Nalmefene Treatment of Alcohol Dependence: Study Methods

- NMF has less dose-dependent liver toxicity, greater oral bioavailability, longer duration of antagonist action, and stronger delta opioid receptor binding than NTX
- 21 M & F alcohol dependent outpatients
  - no drug abuse or serious illness
- Random, double-blind treatment with PBO, nalmefene 10 mg/d, nalmefene 40 mg/d
- 12 weeks medication
- Weekly individual relapse prevention counseling, AA

Mason, Ritvo, Morgan, et al, Alc Clin Exp Res 19

Nalmefene Treatment of Alcohol Dependence: Study Results

- **Adverse Effects: No serious adverse events**
- **Efficacy: 40 mg Nalmefene significantly superior to 10 mg Nalmefene or PBO in:**
  - Relapse rate
  - Percent days abstinent
  - Drinks/drinking day
  - Reduction in ALT

Mason, Ritvo, Morgan, et al, Alc Clin Exp Res 1994

Nalmefene Treatment Study II: Methods

- 105 recently abstinent Alc Dep S's
- Random, double-blind treatment
- PBO, nalmefene 20 mg/d, nalmefene 80 mg/d
- 12 weeks medication
- Weekly individual CBT

Mason, et al., 1999

Nalmefene Treatment of Alcohol Dependence: Study Results

- **Adverse Effects: No serious adverse events**
- **Efficacy: 80 mg Nalmefene significantly equal to 20 mg Nalmefene and superior to PBO in:**
  - Relapse rate at week 1 and thereafter
  - Heavy drinking relapses
  - Post-treatment relapses

Mason, et al, 1999

SSRIs and Buspirone

- RATIONALE
- EFFICACY
- ADVERSE EFFECTS
- EFFECT ON COMPLIANCE

Alcoholism: Psychiatric Co-morbidity

- Major depression: 15-30%
- Bipolar affective disorder: 4-12%
- Panic Disorder: 10-16%
- Social Phobia: 8-12%
- Generalized Anxiety Disorder: 10-25%

Fluoxetine in Alcohol Dependence

- Two negative RCTs in alcohol dependent inpatients and outpatients not selected for concurrent major depression

Kranzler et al., 1995, Kabel and Petty, 1996

Fluoxetine in Suicidal Depressed Alcoholics

- 51 Depressed suicidal alcoholics enrolled in 12-week RCT of fluoxetine vs PBO; fluox. dose 40-60 mg QD
- Fluoxetine significantly superior to PBO in reduction of HAM-D depression scores
- Fluoxetine significantly superior to PBO in reduction of total alcohol consumption.
- Fluoxetine significantly superior to PBO in reduction of marijuana, but not cocaine consumption
- Cocaine abuse/dependence poor prognostic indicator

The great tragedy of science:

the slaying of a beautiful hypothesis by an ugly fact.

Thomas Huxley

Poor Results with Fluoxetine in Type B Alcoholics

- 95 alcoholics enrolled in 12-week RCT of fluoxetine vs PBO; fluox. dose 40-60 mg QD
- 35 Type B and 60 Type A [Babor et al.] subjects
- No evidence of superiority of F vs PBO in entire group
- Type B subjects drank significantly more with fluoxetine than PBO treatment.
- Type A subjects drank similarly with fluoxetine and PBO treatment.

Kranzler et al., 1996

Sertraline in Alcohol Dependence

- 36 Abstinent alcoholics with major depression treated in RCT with 100 mg QD sertraline or PBO. Superior depression outcomes in alcoholics treated with sertraline; No report of drinking outcomes

  Roy, 1998

- 100 abstinent alcoholics treated with 200 mg QD sertralilne or PBO. Superior drinking outcomes among low severity [Type A] but not high severity [Type B] alcoholics

  Pettinatti et al., Alc Clin Exp Res 2000

Buspirone Treatment of Anxious Alcoholics

- 5 Studies; 3 positive, 2 negative
- Neg studies used low intensity of psychosocial treatment [e.g., AA referral] or Rx 3-4 weeks IP TX; positive studies used CBT or TSF
- Superior to PBO for EtOH consumption in doses 45-60 mg QD; 4 of 5 studies found B>PBO in anxiety
- Increased treatment retention in 3 studies
- Well-tolerated: < 1% discontinuation rate.
- No toxicity if alcohol consumed; cf. benzos.

Alcoholics Attitudes Toward Pharmacotherapy for Alcohol Dependence

- Approximately half of 127 patients enrolled in 3 abstinence-oriented treatment programs in RI reported favorable attitude toward use of disulfiram and naltrexone for treatment of alcohol dependence.
- **Strongest predictor of willingness to take medication was a belief that the medication would be helpful.**

Swift et al., 1998

Naltrexone Treatment of Alcohol Dependence in Primary Care

29 alcohol dependent patients treated with 50 mg QD NTX and 10 weeks of brief counseling by PCPs

RESULTS

71% completed treatment

31% relapsed to heavy drinking

Significant decline in heavy drinking days and drinks/drinking day

Significant increase in percent days abstinent

Significant decline in GGT

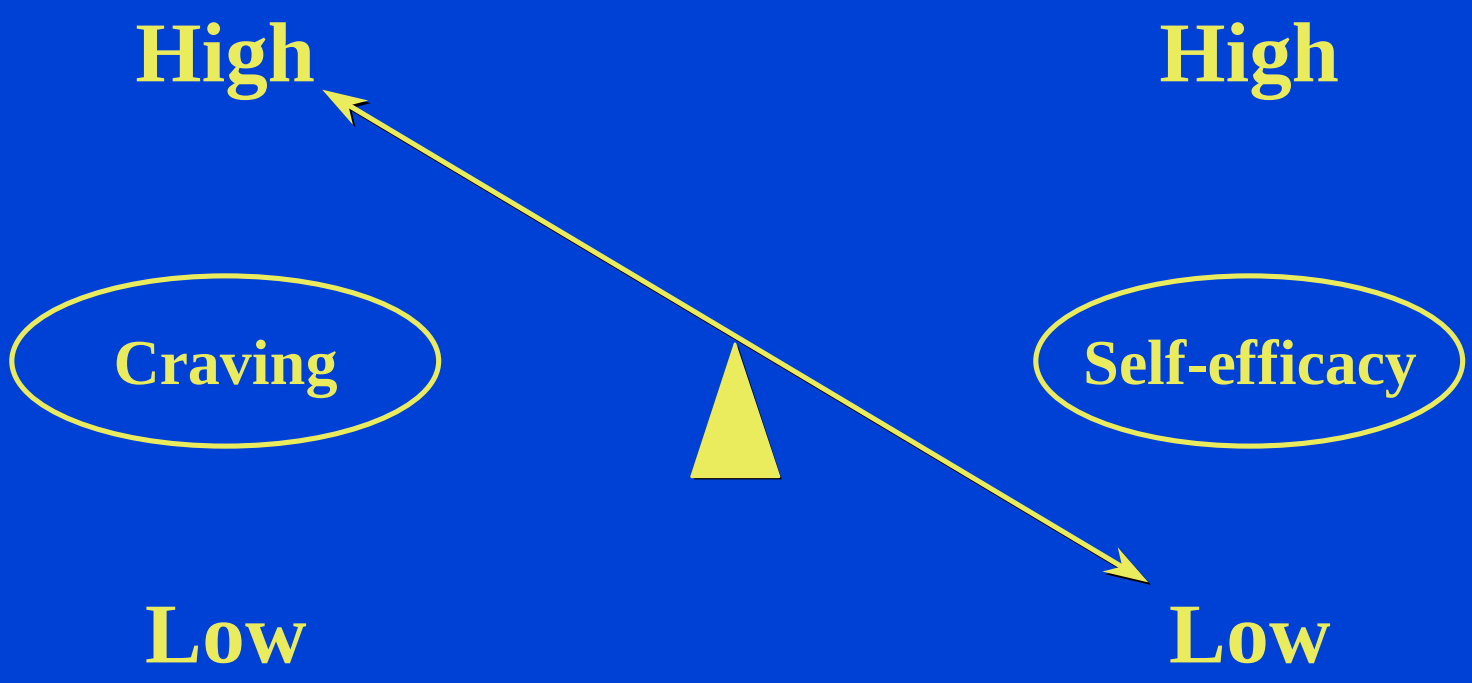
NO Control Group

O'Connor et al., 1997

Why Medications are not the Sole Treatment for Alcoholism

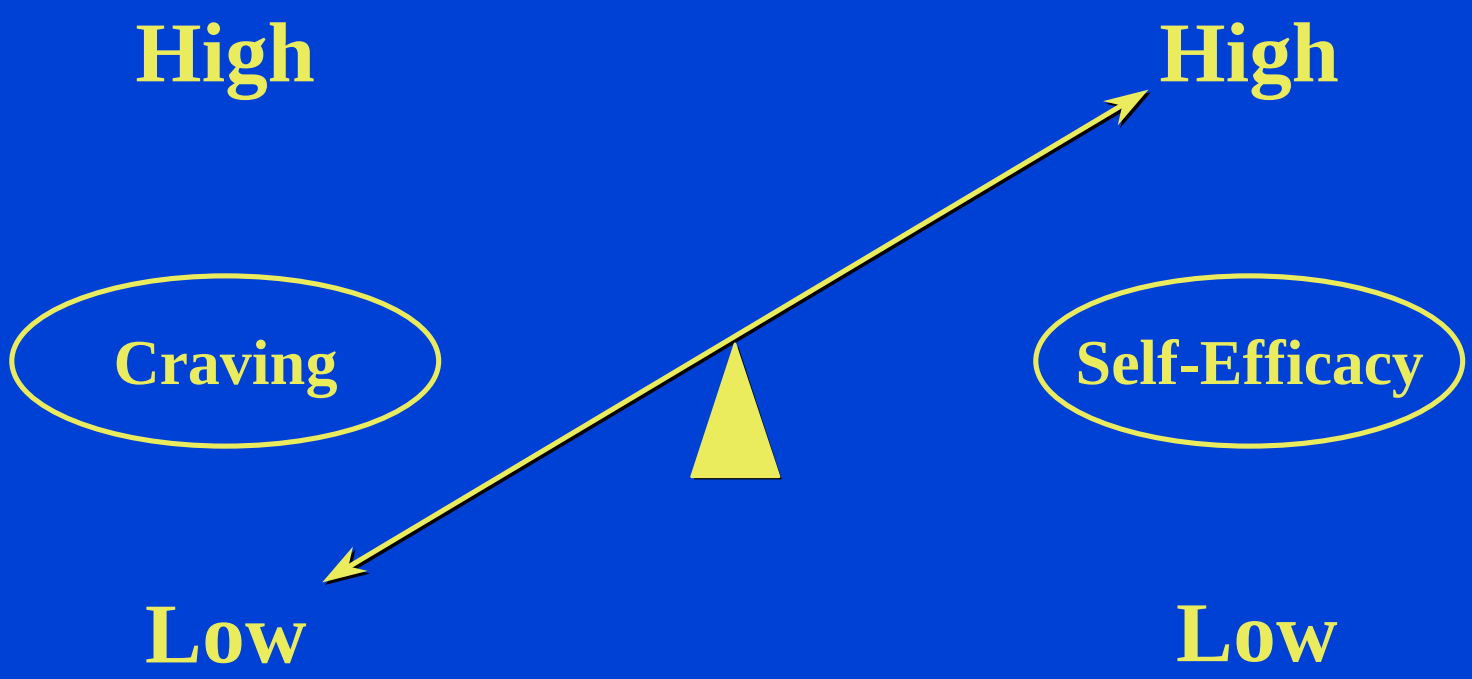
- Variable efficacy
  - Some unhelped
  - Partial effects
- Compliance variable
- Side effects limit compliance
- Effects fall off with treatment cessation
- Treatment efficacy limited to single drug class
- Multidimensionality of alcoholics' problems

Alcohol Dependence



M.J. Bohn and R.F. Anton

Naltrexone Plus Psychosocial Treatments [e.g., Relapse Prevention Therapy]



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Combining Psychosocial and Pharmacotherapy Treatments for Alcoholism

- Medication Effects
  - Reduce craving and responsiveness to cues
  - Reduce reinforcement during an alcohol “slip”
  - Provide a sense of external control over urges and desire
  - Serve as cues for reinforcement of behavioral change
  - Enhance treatment retention by encouraging clinic attendance for refill and check-up
  - Reduce early relapse to maximize goals of therapy

R.F. Anton and M.J. Bohn

Combining Psychosocial and Pharmacotherapy Treatments for Alcoholism

- **Effect of Psychosocial Treatments**
  - **Enhance Rx compliance**
  - **Educate about alcohol's medical, psychological, and social effects**
  - **Increase motivation: abstinence, recovery from slips**
  - **Provide external control & social support for abstinence**
  - **Teach and rehearse relapse prevention and coping skills**
  - **Increase self-efficacy and reward successes**
  - **Provide a routine and conceptual framework for sobriety**
  - **Provide acceptance, and warmth, thereby reducing stigma and enhancing motivation**

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Roles of Psychotherapy

- Set motivation to stop use
- Develop alternatives to alcohol use
- Foster coping skills
- Improve interpersonal functioning
- Enhance affect management
- Prevent relapse
- Enhance Rx compliance and response
- Provide hope and optimism
- Provide information, structure, and a model